REMARKS

The Office Action mailed April 21, 2011 presents the examination of claims 16 and 19-28.

Claim 16 is amended to make minor editorial changes and to affirmatively correct the formula (I). No new matter is introduced by the amendments.

Rejections under 35 USC § 112, second paragraph

Claims 16 and 19-20 are rejected under 35 USC § 112, second paragraph as allegedly being indefinite. The Examiner asserts that it is unclear what is meant by "a sample of the antibody." Notwithstanding that one of ordinary skill in the art has a clear understanding that "a sample of the antibody" would be an aliquot of the "antibody that specifically binds 1α,25-dihydroxy vitamin D having the vitamin D derivative of formula (I) bound thereto", claim 16 is amended to recite that "an amount" of the antibody:vitamin D derivative complex is contacted with some of the measurement sample to effect displacement of the derivative of formula (I) from the complex by 1α,25-dihydroxy vitamin D present in the measurement sample.

Claim 16 is also deemed indefinite in the recitations of two structures for the vitamin D derivative of formula (I). An oversight by Applicants' Representative in formatting of the previously filed paper inappropriately left an incorrect structure intended to be deleted in the claim. Claim 16 is amended to delete the incorrectly drawn structure of the formula (I).

Claim 19 is said to be indefinite in the recitation "wherein said competitive [protein] binding assay is selected from the ... ." The Examiner asserts that it is unclear which of the steps of claim 16 is intended to be described by the phrase "competitive binding assay" and furthermore that none of the steps i), ii) or iii) in claim 16 recite the phrase, "competitive binding assay."

The Examiner has overlooked the term "competitive protein binding assay" in the preamble of claim 16. Applicants submit that this phrase in claim 16 provides antecedent basis for its further definition by various named detection formats in claim 19. One of ordinary skill in the art, who is the audience of the claims, has no difficulty understanding any of the terms presented in claims 16 and 19. This is especially so when the skilled artisan reads the

specification and drawings, which include abundant description of the various versions of competitive assays (*e.g.* Figures 6-13).

The Examiner should further note that claim 16 describes the essence of a competitive assay; that is, an analyte and an added ligand compete for binding to a particular reagent. In claim 16 this is described as competition by the analyte 1α,25-dihydroxy vitamin D with a ligand that is the vitamin D derivative of formula (I) for binding to an antibody that specifically binds 1α,25-dihydroxy vitamin D.

Claim 20 is said by the Examiner to be indefinite in reciting "wherein the method is a sandwich immunoassay." The Examiner asserts that some step recited in claim 16 must be described by a sandwich immunoassay.

Again, the term "sandwich immunoassay" is intended to further limit the term "competitive protein binding assay" in the preamble of claim 16 by describing a specific format for such an assay. One of ordinary skill in the art well-understands the arrangement of the reagents and the particularized steps for employing them to perform a competitive protein binding assay in a "sandwich" format, and indeed such is illustrated in the specification at, *e.g.* at page 15 and in Figures 9 and 10.

Applicants submit that the claims are not at all indefinite, and thus the instant rejection should be withdrawn.

Rejection under 35 USC § 112, first paragraph

Claims 16 and 19-20 are rejected under 35 USC § 112, first paragraph for alleged lack of written description support for the breadth of a "material that specifically binds 1α,25 hydroxy vitamin D." This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner asserts that the phrase, "material that binds 1α,25-dihydroxy vitamin D" encompasses many materials, such as a microtiter plate having bound thereto an antibody specific for 1α, 25-dihydroxy vitamin D, but the specification only teaches purification using an Extrelut™ column followed by silica gel chromatography.

Applicants submit that the purification of 1α,25-dihydroxy vitamin D using an Extrelut[tm] column followed by silica gel chromatography is simply one example of a method that can be applied. The Examiner is reminded that a specification need not disclose that which is already known to a person of ordinary skill in the art at the time the application was filed (*see, e.g., Paperless Accounting, Inc. v. Bay Area Rapid Transit System,* 231 USPQ 649 (Fed. Cir. 1986)) and also that it is very well-settled that the claims need not be limited to the embodiments specifically exemplified in the specification (*see, e.g., In re Gay*, 135 USPQ 311 (CCPA 1962).

Thus, Applicants point out that at the time the present application was filed, the skilled artisan knew of methods other than purification by chromatography over Extrelut[tm] column followed by silica gel chromatography for separating 1α,25-dihydroxy vitamin D from other derivatives of vitamin D. For example, the specification discloses an antibody that specifically binds 1α,25-dihydroxy vitamin D (Mawer et al.) and the skilled artisan would know how to utilize such antibody in an affinity chromatography technique. Also, DeLuca EP'945, cited by the Examiner in making a rejection over prior art, describes materials and methods for adsorption and separation of 25-hydroxy vitamin D from 1 α,25-dihydroxy vitamin D, for example:

column 3, lines 1-2:

... *is* purified *on a* silica column *to* separate *out* interfering *vitamin* D metabolites...,

column 3, lines 24-26

...it should be noted that a Sep-Pak silica column purification is preferably performed to remove potentially interfering vitamin D metabolites...

column 3, lines 28 to 32

.... Other columns such as Sephadex LI-120 or Lipidex5000 can be used instead of Sep-Pak to separate la,25-dihydroxy vitamin D from 25-hydroxy vitamin D and 24,25-dihydoxy vitamin D.

column 5, lines 12 to 40,

Here there is an entire example of sample extraction and chromatography. The Sep-Pack silica chromatography can further be done according to the method of T.Reinhardt et al., J Clin Endocrinol. Metab. (1984) 91-98. Alternative extraction methods are further described at column 5, line 44 to column 6, line 20.

It is not the law that patent claims must be limited to exemplary embodiments and also one of ordinary skill in the art was aware at the time of filing of the present application of methods for separating 1α,25-dihydroxy vitamin D from other vitamin D derivatives in biological samples. Therefore, the Examiner's assertion that the claims must be limited in the method for separating 1α,25-dihydroxy vitamin D to chromatography over Extrelut^{tm} followed by silica gel chromatography is inappropriate and the instant rejection should be withdrawn.

Rejection for obviousness

Claims 16, 19-25 and 28 are rejected under 35 USC § 103(a) as unpatentable over DeLuca EP '945 in view of Mawer (1985) and Holick WO '127. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants submit that the Examiner fails to establish *prima facie* obviousness of the claimed invention and also that the record contains evidence sufficient to establish unobviousness of the invention over the prior art cited.

The Examiner does not establish prima facie obviousness

A proper case of *prima facie* obviousness requires that the collection of references cited disclose or suggest each and every feature recited in the claims and that one of ordinary skill in the art would have a reasonable expectation of success in accomplishing the invention from reading the collected references. In the present instance, claim 16 recites a step of displacing the derivative of 1α,25-dihydroxy vitamin D having the formula (I) from an antibody that is specific for 1α,25-dihydroxy vitamin D. Such a step is not disclosed or suggested by either of Deluca EP '945 or Holick WO '127, both of whom disclose displacement from Vitamin D Receptor.

Mawer (1985) is cited by the Examiner only for disclosure of antibody that specifically binds to 1α,25-dihydroxy vitamin D. The Examiner does not point out any part of Mawer (1985) that discloses displacement of derivative of 1α,25-dihydroxy vitamin D from that antibody by any analyte.

As noted, instead of Vitamin D Receptor, the present invention uses a monoclonal antibody against 1a,25-hydroxy vitamin D as the binding protein. The complementarity-determining regions of the monoclonal antibody that bind to 1a,25-hydroxy vitamin D are different from the vitamin D binding portion of VDR, and so the manner of binding of 1a,25-hydroxy vitamin D to these two proteins would be different.

Thus, Applicants submit that the combined references do not establish at all that 1α,25-dihydroxy vitamin D would successfully displace the derivative of formula (I) from anti-1α,25-dihydroxy vitamin D antibody in a manner sufficient to provide a useful assay, especially in view of the disclosure of Holick WO '127 that such a compound or a similar one (as the Examiner asserts) is displaced from Vitamin D Binding Protein with an efficiency of only 1:11.

These reasons alone are sufficient to defeat the Examiner's assertion of *prima facie* obviousness. To them, Applicants will add that the compound of the formula (I) is not the compound synthesized by Holick WO '127, as has been repeatedly argued in the prosecution. (*See, e.g.*, Applicants' paper of October 31, 2008, at pages 9-11.)

Holick WO '127 describes a biotinylated **1a,25-dihydroxy** vitamin D (example 9, compound G of Figure 6) which is an **ester**. (The ether derivatives in Holick WO '127 are of 25-hydroxy vitamin D.) An ester derivative was chosen due to the more complicated synthesis since the 1a-hydroxy group was first protected as a tert-butyldimethylsilyl ether (TBDMS). The DCC-coupling of the TBMS-protected compound with FMOC-caproic acid produces an ester linkage as correctly shown in Figure 6. Consequently, Holick WO '127 teaches a biotinylated 1α,25-dihydroxy vitamin D ester derivative to be used in a competitive binding assay.

On the other hand, the biotin-labelled vitamin D derivative of the invention comprises an **ether** linker, and so a different compound.

Applicants have also provided objective evidence of unobviousness of the present invention compared to the embodiment disclosed by the cited references, in particular providing a lower limit of detection of the 1α,25-dihydroxy vitamin D analyte. The Examiner is referred to Applicants' paper of October 31, 2008, at page 12. The Examiner has not as yet ever explained why these results are not persuasive of unobviousness of the invention. Accordingly, Applicants submit that this evidence stands as sufficient to show unobviousness of the present invention and the instant rejection should be withdrawn.

Claim 27 is rejected under 35 USC § 103(a) as being unpatentable over DeLuca EP '945 in view of Mawer (1985), Holick WO '127 and DeLuca '770. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The failure of the combination of DeLuca EP '945, Mawer (1985) and Holick WO '127 to establish *prima facie* obviousness of the basic invention has been explained above. DeLuca '770 is cited only for the feature of immobilization on magnetic beads. This reference does not remedy the deficiencies of the other references to establish *prima facie* obviousness, nor does it add any disclosure that effectively refutes the evidence of unexpected results obtained by the present invention. Therefore, claim 27 is patentable over the combined references for the same reasons as explained above, and the instant rejection should be withdrawn.

Applicants believe the pending application is in condition for allowance, and such favorable action is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Ph.D., Reg. No. 36,623, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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